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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/567,073	03/07/2006	Philip N. Bryan	4115181	2283

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EXAMINER	
MOORE, WILLIAM W	
ART UNIT	**PAPER NUMBER**
1656	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/567,073	BRYAN, PHILIP N.	
	Examiner	Art Unit	
	William W. Moore	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *7 March 2006*.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-61* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Restriction is required under 35 U.S.C. §§ 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group 1, claims 1-17 and 46-49, drawn to a first product, a nucleic acid construct encoding a fusion polypeptide comprising a first fusion partner that is a prodomain polypeptide modified to have an increased affinity for a protease, said first fusion partner operably linked to a second fusion partner which is a polypeptide "of interest", to vectors and host cells comprising the nucleic acid construct, and to a first method of use of the nucleic acid construct, and/or vectors and host cells comprising same, in a recombinant process of making the encoded fusion polypeptide, and to the encoded product.

Group 2, claims 18-27 and 59, drawn to a first method of use of a second product, which may be any of at least nine species of subtilisin, in purifying a polypeptide "of interest" by contacting the fusion polypeptide with the protease to liberate the polypeptide "of interest" and subsequently isolating the polypeptide "of interest".

Group 3, claims 28-38 and 60, drawn to second method of use of the second product, which may be any of at least nine species of subtilisin, in an assay to detect the presence of a "substance of interest" by contacting the second product with a fusion polypeptide comprising a polypeptide of interest to permit the liberation of a polypeptide "of interest" and its subsequent binding of a "substance of interest", and then recovering the complex of the polypeptide and substance "of interest".

Group 4, claims 39-45 and 61, drawn to third product, a drug delivery complex comprising a subtilisin prodomain fused to a drug of interest and further comprising an associated protease, which may be any of at least nine species of subtilisin.

Group 5, claims 46-49, drawn to fourth product, a nucleic acid construct having a coding sequence encoding a fusion polypeptide comprising a first fusion partner that is a polypeptide capable of generating affinity with a protease, said first fusion partner operably linked to a second fusion partner which is a polypeptide "of interest",

Group 6, claims 50-53, drawn to a fifth product, a protease variant capable of specifically hydrolyzing a fusion polypeptide upon the addition of a chemical trigger to liberate a polypeptide of interest and to a method of use thereof in hydrolyzing a fusion polypeptide that need not comprise a prodomain to liberate a polypeptide of interest by contacting the

fusion polypeptide with the protease variant capable of specifically hydrolyzing a fusion polypeptide upon the addition of a chemical trigger in the presence of a chemical trigger.

Group 7, claims 54-58, drawn to a fifth product which is a nucleic acid construct having a coding sequence encoding a fusion polypeptide comprising a first fusion partner that is a peptide modified to have an increased affinity for a protease, said first fusion partner operably linked to a second fusion partner which is a polypeptide "of interest" and to a method of use thereof in a recombinant method of making the encoded fusion polypeptide.

The inventions listed as Groups 1-7 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The inventions of Groups 1 and 2 share no special technical feature because the special technical feature of the invention of Group 1 is a coding sequence in a polynucleotide construct that specifies a prodomain polypeptide modified to have an increased affinity for a protease than a native prodomain and the special technical feature of the invention of Group 2 is a method of requiring that a protease contact a fusion polypeptide comprising a prodomain and a polypeptide, form a complex with the fusion polypeptide, cleave the prodomain from its fusion partner, and further requiring the subsequent purification of the fusion partner. Thus the inventions of Group 1 and Group 2 have no same or corresponding special technical feature.

The inventions of Groups 1 and 3 share no special technical feature because the special technical feature of the invention of Group 1 is a coding sequence in a polynucleotide construct that specifies a prodomain polypeptide modified to have an increased affinity for a protease than a native prodomain and the special technical feature of the invention of Group 3 is a method of assaying for the presence of a substance of interest in a test sample special requiring that a protease contact a fusion polypeptide comprising a prodomain and a polypeptide capable of being a binding partner of a substance of interest that does bind to a substance of interest unless cleaved from the fusion polypeptide, form a complex with the fusion polypeptide, cleave the prodomain from its fusion partner, and further requiring the subsequent purification of the fusion partner bound, or not bound, to a substance of interest. Thus the inventions of Group 1 and Group 3 have no same or corresponding special technical feature.

The inventions of Groups 1 and 4 share no special technical feature because the special technical feature of the invention of Group 1 is a coding sequence in a polynucleotide construct that specifies a prodomain polypeptide modified to have an increased affinity for a protease than a native prodomain and the special technical feature of the invention of Group 4 is a composition of matter requiring that a covalent bond be formed between a prodomain and a drug that need not be a polypeptide, and further requiring the formation of a complex between

the fused composition of matter and protease. Thus the inventions of Group 1 and Group 4 have no same or corresponding special technical feature.

The inventions of Groups 1 and 5 share no special technical feature because the special technical feature of the invention of Group 1 is a coding sequence in a polynucleotide construct that specifies a prodomain polypeptide modified to have an increased affinity for a protease than a native prodomain fused by a peptide bond to a polypeptide fusion partner and the special technical feature of the invention of Group 5 is a coding sequence in a polynucleotide construct that specifies a protein that need not be a prodomain fused by a peptide bond to a polypeptide fusion partner. Thus the inventions of Group 1 and Group 5 have no same or corresponding special technical feature.

The inventions of Groups 1 and 6 share no special technical feature because the special technical feature of the invention of Group 1 is a coding sequence in a polynucleotide construct that specifies a prodomain polypeptide modified to have an increased affinity for a protease than a native prodomain fused by a peptide bond to a polypeptide fusion partner and the special technical feature of the invention of Group 6 is a protease modified to hydrolyze a fusion protein upon contact with a chemical trigger. Thus the inventions of Group 1 and Group 6 have no same or corresponding special technical feature.

The inventions of Groups 1 and 7 share no special technical feature because the special technical feature of the invention of Group 1 is a coding sequence in a polynucleotide construct that specifies a prodomain polypeptide modified to have an increased affinity for a protease than a native prodomain fused by a peptide bond to a polypeptide fusion partner and the special technical feature of the invention of Group 7 is a nucleic acid construct encoding a fusion polypeptide comprising a first fusion partner that is a peptide, which need not be a prodomain, said first fusion partner operably linked to a second fusion partner which is a polypeptide "of interest". Thus the inventions of Group 1 and Group 8 have no same or corresponding special technical feature.

The inventions of Groups 2 and 3 share no special technical feature because the special technical feature of the invention of Group 2 is a method of purifying a polypeptide "of interest" and the special technical feature of the invention of Group 3 is a method of assaying for the presence of a substance "of interest" in a sample. Thus the inventions of Group 2 and Group 3 have no same or corresponding special technical feature.

The inventions of Groups 2 and 4 share no special technical feature because the special technical feature of the invention of Group 2 is a method of purifying a polypeptide "of interest" and the special technical feature of the invention of Group 4 is a complex formed by a subtilisin

prodomain fused to a drug of interest and comprising as well an associated protease. Thus the inventions of Group 2 and Group 4 have no same or corresponding special technical feature.

The inventions of Groups 3 and 4 share no special technical feature because the special technical feature of the invention of Group 3 is a method of assaying for the presence of a substance "of interest" in a sample and the special technical feature of the invention of Group 4 is a complex formed by a subtilisin prodomain fused to a drug of interest and comprising as well an associated protease. Thus the inventions of Group 3 and Group 4 have no same or corresponding special technical feature.

The inventions of Groups 2-4 share no special technical feature with the inventions of Groups 5 and 7 because the special technical feature of the inventions of Groups 2-4 is a method of use of a protease, or the presence of a protease in a complex with a fusion construct comprising a drug, while the special technical features of the inventions of Groups 5 and 7 do not require the use of a protease, or the presence of a protease in a complex with a further compound. Thus the inventions of Groups 2-4 have no same or corresponding special technical feature with the inventions of Groups 5 and 7.

The inventions of Groups 2-4 share no special technical feature with the invention of Group 6 because the special technical feature of the inventions of Groups 2-4 is a method of use of a protease, or the presence of a protease, capable of hydrolyzing a fusion polypeptide comprising a prodomain, while the special technical feature of the invention of Group 6 is a method of use of a protease capable hydrolyzing a fusion polypeptide that need not comprise a prodomain in the presence of a chemical trigger. Thus the inventions of Groups 2-4 have no same or corresponding special technical feature with the invention of Group 6.

The inventions of Groups 5 and 6 share no special technical feature, because the special technical feature of the invention of Group 5 is a nucleic acid construct having a coding sequence encoding a fusion polypeptide comprising a first fusion partner that is a polypeptide capable of generating affinity with a protease, while the special technical features of the inventions of Groups 6, 7, and 9 require no nucleic acid construct having any coding sequence. Thus the invention of Group 5 has no same or corresponding special technical feature with the inventions of Groups 6, 7, and 9.

The invention of Groups 5 and 7 share no special technical feature because the special technical feature of the invention of Group 5 is a nucleic acid construct having a coding sequence specifying a fusion polypeptide comprising a first fusion partner that is a polypeptide capable of generating affinity with a protease, while the special technical feature of the invention of Group 7 is a nucleic acid construct having a coding sequence specifying a peptide modified

to have an increased affinity for a protease. Thus the invention of Group 5 has no same or corresponding special technical feature with the invention of Group 7.

The invention of Groups 6 and 7 share no special technical feature because the special technical feature of the invention of Group 6 is a method of use of a protease to hydrolyze a fusion polypeptide that need not comprise a prodomain to liberate a polypeptide of interest, while the special technical features of the invention of Group 7 does not require the use of a protease. Thus the invention of Group 6 has no same or corresponding special technical feature with the invention of Group 7.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

The species are as follows:

1. Methods practiced with, or products comprising, the S149 subtilisin species.
2. Methods practiced with, or products comprising, the S160 subtilisin species.
3. Methods practiced with, or products comprising, the S188 or S191 subtilisin species.
4. Methods practiced with, or products comprising, the S189, S190, S196, S197, S198, S199, or S201 subtilisin species.
5. Methods practiced with, or products comprising, the S193 or S202 subtilisin species.
6. Methods practiced with, or products comprising, the S194 subtilisin species.

Applicant is required, in reply to this action, to elect a single species to which the claims shall be restricted if no generic claim is finally held to be allowable. The reply must also identify the claims readable on the elected species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered non-responsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

The claims are deemed to correspond to the species listed above in the following manner:

Claims 18-38, 53, 59, and 60 are drawn to methods that might be practiced with any of the nine species of modified subtilisins of the nine species of subtilisins disclosed herein that are listed in claims 25 and 26. Claims 39-45, 50-52 and 61 are drawn to products, and to a system,

that may comprise any of the nine species of subtilisins disclosed herein that are listed in claims 25 and 26.

The following claims are generic: 18-45, 50-53, and 59-61.

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons:

The S149 subtilisin species disclosed to be useful in methods and systems claimed herein is disclosed in Table 1 of the prior art publication US 6,541,234, made of record herewith, thus there is no unity of invention among species of a genus where a member of the genus is present in the prior art.

The S160 subtilisin species has amino acid sequence modifications at two positions further to those of the S149 species disclosed in Table 1 of the prior art publication US 6,541,234, thus has a technical feature absent from the S149 subtilisin species.

The S188 and S191 subtilisin species has amino acid sequence modifications at two positions further to those of the S149 species disclosed in Table 1 of the prior art publication US 6,541,234, and a further amino acid sequence modification at a position not modified in the S160 subtilisin, position N155, thus both have a technical feature absent from each of the S149 and S160 subtilisin species.

The S189, S190, S196, S197, S198, S199, and S201 subtilisin species have amino acid sequence modifications at two positions further to those of the S149 species disclosed in Table 1 of the prior art publication US 6,541,234, and a further amino acid sequence modification at a position not modified in either of the S160 or S188 subtilisin species, position D32, thus all have a technical feature absent from each of the S149, S160, and S188 subtilisin species.

The S193 and S202 subtilisin species have amino acid sequence modifications at two positions further to those of the S149 species disclosed in Table 1 of the prior art publication US 6,541,234, and a further amino acid sequence modification at a position not modified in any of the S160, S188, S189, S190, S191, S196, S197, S198, S199, and S201 subtilisin species, position S166, thus both have a technical feature absent from each of the S160, S188, S189, S190, S191, S196, S197, S198, S199, and S201 subtilisin species.

The S194 subtilisin species has amino acid sequence modifications at two positions further to those of the S149 species disclosed in Table 1 of the prior art publication US 6,541,234, and a further amino acid sequence modification beyond those of the S160 subtilisin that is not present in any of the S160, S188, S189, S190, S191, S193, S196, S197, S198, S199, S201, or S202 subtilisin species, position S221, thus has a technical feature absent from each of the S160, S188, S189, S190, S191, S193, S196, S197, S198, S199, S201, and S202 subtilisin species.

Inventorship

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the

application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee withdrawn required under 37 CFR 1.17(i).

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is 571.272.0933 and whose FAX number is 571.273.0933. The examiner can normally be reached Monday through Friday between 9:00AM and 5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisory Primary Examiner, Dr. Kathleen Kerr Bragdon, can be reached at 571.272.0931. The official FAX number for all communications for the organization where this application or proceeding is assigned is 571.273.8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571.272.1600.

/Nashed/
Nashaat T. Nashed, Ph.D.
Primary Examiner, Art Unit 1656

William W. Moore
15 November 2007